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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

7590 12/07/2006

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EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-11,13,14,16,17 and 50-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-11,13,14,16,17 and 50-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 09/22/2006, and a response to the arguments is set forth.

2. Claims 5, 6, 12, 15 and 18-49 have been cancelled

3. Claims 7, 50 and 56 have been amended.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior office action.

5. It is noted that applicant indicates that the "...office action communication dated October 4, 2000 states that upon reconsideration, the restriction would be vacated.." (page 7 of the response).

The applicants argument is considered proper and hence the method claims, claims 57-69 are examined along with claims 1-4, 7-11, 13, 14, 16, 17, 50-56 and 70-72.

Thus, claims 1-4, 7-11, 13, 14, 16, 17 and 50-72 are under examination.

Rejections Withdrawn

6. The rejection of claims 50-56, 71 and 72 under 35 U.S.C. 112, first paragraph is withdrawn in view of amendments to the claims.

7. The rejection of claims 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Rejections Maintained and Response to Arguments

8. The rejection of claims 1-4, 7-11, 13-14, 16-17, 22-26, 29-32, 50-56 and the newly added claims 70-72 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989), Cabilly et al (U.S Patent 4816567, issued 3/89), Boss et al (U.S Patent 4816397, issued 3/89), Robinson et al (U.S. Patent 5618920, filed 4/94), Ward et al (Nature 341:544-546, 1989), and Huston et al (U.S. Patent 5258498, issued 11/93) is maintained.

The applicant argues (page 8-9 of the response filed on 09/22/2006) "the Fitzgerald Deceleration.... Asserts to the fact that the finding that RFB4 immunotoxins retain the binding specificity and affinity of the parent RFB4 is unusual.....the mere teachings that a composition could possibly have a characteristic does not lead to the logical condition that all of such compositions would have that characteristic....the examiner provides no evidence or reasoning as to why one of skill could predict such superior properties based on the cited art.

The applicant is respectfully reminded that The Declaration of Dr. Fitzgerald has been carefully considered but is deemed not to be persuasive. The declaration states that previous LL2-PE38 immunoconjugates were poorly cytotoxic and did not express well which is in contrast to the RFB4 conjugate and the high level of expression, retention of binding, superior toxicity of the RFB4ds(FV)-PE38 is surprising and can not be predicted from the art. In response to this argument, as stated previously the art did recognize dsFV as superior and Reiter et al (Nature Biotech) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column). The Reiter et al (Biochemistry) clearly shows better cytotoxicity for the dsFV as compared to the scFv and better expression yields (see Table 1) and better stability (see Table 2) and teach "that dsFv's have at least the same binding properties as scFv's, and in some cases they may be better" (see abstract) and Reiter et al teach that scFv can retain the specificity and affinity of IgG (see page 5451). In addition, because the dsFv have superior characteristics over the scFv they would obviously be chosen over scFv and in addition Shen et al teach that the Fab'-RFB4 bound 1.2 to 3.5 times more stronger than other Fab' fragments an the potent cytotoxic activity of the RFB4-AS appears to derive from their superior binding affinity and the art recognizes the superiority of this antibody. Thus, there is clear teaching and evidence, wherein Both Reiter et al (Biochemistry) and Kuan et al (Biochemistry) show dsFvs that are active and potent and as such one skill in the art would have a reasonable expectation of success in making the claimed immunoconjugate dsFv with the RFB4 antibody.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

New Grounds of Rejections

9. Claims 57-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96).

The instant claims are drawn to a method for inhibiting the growth of a malignant B-cell that express a CD22 molecule on the surface of the cell, said method comprising contacting said malignant B-cell with an effective amount of a recombinant immunoconjugate comprising a therapeutic agent or a detectable label covalently linked to an RFB4 disulfide-stabilized Fv (dsFv) having a variable heavy chain (VH) comprising SEQ ID NO:2 in which a Cys residue is substituted for Arg at position 44; and a variable light chain (VL) comprising SEQ ID NO:4 in which a Cys residue is substituted for Gly at position 100, thereby inhibiting the growth of the malignant B-cell, wherein said therapeutic agent is a Pseudomonas exotoxin (PE) or a cytotoxic fragment, wherein said cytotoxic fragment is PE38, wherein said variable heavy chain is covalently linked at the carboxyl terminus of said therapeutic agent, wherein said VH chain is covalently linked to said VL chain through a linker peptide, wherein said VH

chain is linked to said VL chain through a cysteine-cysteine disulfide bond, wherein said linker peptide has the sequence of SEQ ID NO:5, wherein said malignant B-cell is contacted *in vivo*, wherein said malignant B-cell is selected from the group consisting of: a rodent B-cell, a canine B-cell, and a primate B-cell, wherein said malignant B cell is a chronic lymphocytic leukemia cell, wherein said malignant B cell is a hairy cell leukemia cell, wherein said malignant B cell is a prolymphocytic leukemia cell, wherein said malignant B cell is a B cell lymphoma cell.

Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth B-cell lymphomas in mice. Ghetie et al does not teach an anti-CD22 antibody with a VH with a cysteine at position 44 or a VL with a cysteine at position 100 conjugated to a cytotoxic fragment of PE wherein the VH is linked to the PE at the carboxyl terminus, and the VH and VL are linked through a peptide linker that has SEQ ID NO:5 or a disulfide bond, or a method of inhibiting the growth of malignant B-cells with a anti-CD22 antibody PE conjugate, including the various types of B-cell malignancies. These deficiencies are made up for in the teachings of Shen et al, Reiter et al and Kuan et al.

Shen et al teach the hybridoma which produces the RFB4 antibody (see Antibodies under Material and Methods on page 792) and the RFB4 antibody can be a Fab' and the RFB4 antibody is the choice for preparing Fab' immunotoxins (see abstract). Shen et al also suggests (pages 795-796 Discussion, in particular) that the unusually potent cytotoxic activity of said antibody would be excellent candidates for the

systemic therapy of $CD22^+$ human B-cell neoplasm; for example in B-cell lymphomas, hairy-cell leukemia and B-cell chronic lymphocytic leukemia in addition to making effective reagents for the in vivo therapy of $CD22^+$ B cell lymphomas and leukemia in humans.

Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL. The antibody is conjugated to a toxin of PE38. Reiter et al teach a general method for producing disulfide-stabilized immunotoxins (see page 5453, Results).

Kuan et al teach a disulfide stabilized Fv directed to a cancer antigen. Huan et al teach that the variably heavy chain domain is inserted near the carboxyl terminus of PE (abstract lines 3-4 in particular) and that the VH and VL are linked through a sequence that has SEQ ID NO:5 and through a disulfide bond and expression cassettes; in addition to that the method produces more stable dsFV immunotoxins.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for inhibiting the growth of a malignant B-cell that express a CD22 molecule on the surface of the cell.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced the method for inhibiting the growth of a malignant B-cell that express a CD22 molecule on the surface of the cell because Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain

and inhibition of growth B-cell lymphomas in mice because Shen et al teach the hybridoma which produces the RFB4 antibody which can for preparing Fab' immunotoxins and suggest that the unusually potent cytotoxic activity of said antibody/immunotoxins would be excellent candidates for the systemic therapy of $CD22^+$ human B-cell neoplasm; for example in B-cell lymphomas, hairy-cell leukemia and B-cell chronic lymphocytic leukemia in addition to making effective reagents for the in vivo therapy of $CD22^+$ B cell lymphomas and leukemia in humans.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have produced the method as claimed using the antibodies as claimed because Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth B-cell lymphomas in mice and Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL, wherein the antibody is conjugated to a toxin of PE38; in addition to teaching that VH is linked to the amino terminus of PE38 and a general method for producing disulfide-stabilized immunotoxins.

Further, it would have been obvious to one of ordinary skill in the art and one would have been motivated and had a reasonable expectation of success to have produced the claimed method by combining the teachings of Ghetie et al, Shen et al and Reiter et al with that of Kuan et al because Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth B-cell lymphomas *in vivo*, and Shen et al teach the RFB4 and suggest that such antibody/immunotoxins would be

excellent candidates for the systemic therapy of $CD22^+$ human B-cell neoplasm; for example in B-cell lymphomas, hairy-cell leukemia and B-cell chronic lymphocytic leukemia in addition to making effective reagents for the in vivo therapy of $CD22^+$ B cell lymphomas and leukemia in humans, and Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL, which is conjugated to a toxin of PE38 and because Kuan et al teach that the variably heavy chain domain is inserted near the carboxyl terminus of PE and that the VH and VL are linked through a sequence that has SEQ ID NO:5 and through a disulfide bond and expression cassettes; in addition to that the method produces more stable dsFV immunotoxins.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claims are allowed

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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Sheela G. Huff
SHEELA HUFF
PRIMARY EXAMINER